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Subthalamic Nucleus Influences Spatial Orientation in Extrapersonal Space

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Abstract: While the role of frontal and parietal cortex in spatial orientation has been studied extensively, the contribution of the basal ganglia and especially the subthalamic nucleus to spatial orientation remains less clear. Here we use subthalamic nucleus (STN) deep brain stimulation (DBS) in Parkinson's disease (PD) as a reversible model of functional lesioning to evaluate the influence of the STN in extrapersonal space orientation. To this end, 12 PD patients were examined 1 year after implantation of DBS electrodes in the STN after overnight withdrawal of L-dopa. Patients were tested in a pseudorandomized order while both stimulators, the right only, the left only, or no stimulator, were switched on. Patients performed line bisection and a reaction time task responding to stimuli of the middle, the left, and the right extrapersonal space. A separate assessment of the right and left hand responding to visual stimuli in each hemispace

Contralesional neglect in humans is most commonly the consequence of temporoparietal lesions in the right hemisphere.^{1–5} But neglect may also occur after lesions to other regions, including areas in the frontal lobe.^{3,6–10} Various studies have documented that lesions restricted to the right basal ganglia lead to an asymmetry in space exploration and a failure to react or respond to stimuli located in the contralateral hemispace.^{2,11–18} Most of these studies examine patients with neglect as a consequence of stroke and it has been controversial if hemispatial neglect following subcortical lesions are the conmade it possible to distinguish hemispatial and hemimotor impairments. No asymmetries in space orientation were found when both stimulators were switched OFF, when both stimulators were switched ON, and when only the right stimulator was switched ON. When only the left subthalamic stimulation was switched ON, the reaction times of both hands to visual stimuli in the left extrapersonal hemispace increased significantly and the line bisection test showed a significant orientation to the right. These results lead to the conclusion that the STN and its cortical projections influence the network involved in visuospatial orientation. These patterns of symptoms of neglect demonstrate the influence of the STN on the attentional system of the nondominant hemisphere. © 2005 Movement Disorder Society

Key words: subthalamic nucleus; deep brain stimulation; spatial orientation; neglect

sequence of associated cortical dysfunction not visible by structural computer tomography or conventional magnetic resonance imaging (MRI).^{15,19,20} In support of this hypothesis, several studies have shown cortical hypoperfusion in patients with neglect associated with subcortical stroke using MR perfusion-weighted imaging or single photon emission computed tomography (SPECT).^{15,19,21}

It has been demonstrated that monkeys with unilateral lesions of nigrostriatal dopamine projections exhibited a persistent neglect of contralesional space. Rats with unilateral 6-hydroxydopamine injections destroying dopaminergic projection from the substantia nigra show a disturbance in space orientation, asymmetries in head position, and a change in response behavior to visual and tactile stimuli comparable to symptoms of neglect of contralateral stimuli.²² Additional lesioning of the sub-thalamic nucleus (STN) improves some of these deficits.²²

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Although the mechanisms of bilateral deep brain stimulation (DBS) of the STN are not well understood, the functional outcome of subthalamic stimulation mimics that of an STN lesion.^{23,24} Previous studies have used acute effects of STN DBS as a tool to modify the activity in basal ganglia circuits intraindividually.^{25–30}

To evaluate the possible influence of STN stimulation on spatial orientation, we assessed 12 patients with Parkinson's disease (PD) after implantation of electrodes in the STN for chronic DBS in four conditions: turning both stimulators OFF, turning ON only the right stimulator, turning ON only the left stimulator, and turning ON both stimulators. After overnight withdrawal of L-dopa, patients were pseudorandomly assigned to one of the stimulation conditions. Patients performed a line bisection and a reaction time task responding to stimuli of the middle, the left, and the right extrapersonal space developed by Sakashita.³¹ A separate assessment of the right and left hand responding to visual stimuli in each hemispace made it possible to distinguish hemispatial and hemimotor impairments. Additionally, a standardized motor score was performed [Unified Parkinson Disease Rating Scale, part III (UPDRS III)].

PATIENTS AND METHODS

Patients

A consecutive series of 12 PD patients, 4 female and 8 male (mean age, 57.6 ± 6.1 years), were examined 6 to 25 month (mean, 13 ± 6.7 months) after bilateral electrode implantation into the STN for chronic DBS in Kiel, Germany. All PD patients fulfilled the brain bank criteria for PD32 and all patients suffered from advanced PD with a mean disease duration of 12 ± 4.8 years. None of them was demented preoperatively and postoperatively (Mattis Dementia Rating Scale Score $> 130^{33}$). Seven patients were predominantly left-sided and five patients were predominantly right-sided preoperatively. The neurological examination excluded deficits in the visual field. All patients had a normal vision or a vision corrected to normal. All subjects were right-handed as assessed by Annett's test of handness.³⁴ The stimulating electrodes (Medtronic, Minneapolis, MN) were implanted using stereotactic MRI-based targeting and intraoperative electrophysiology with microrecording and microstimulation as previously described.35 Three patients are included in a study visualizing the most effective stimulation electrode in the border part of the STN.36 The preoperative MRI did not show any large vessel infarction. Three patients had small white matter lesions of microvascular origin. At the time of testing, patients received an average levodopa equivalent daily dosage of 419 \pm 140 mg and stimulation characteristics were as follows: monopolar stimulation of a single electrode contact on the right side, mean pulse width of 62 \pm 8.7 μ s, frequency of 130, and mean stimulation voltage of 3.0 \pm 0.6 V; for the left side, mean pulse width of 65 \pm 17 μ s, frequency of 130 Hz, and mean stimulation voltage of 3.1 \pm 0.5 V. The protocol was approved by the ethics committee at Kiel University and all patients gave informed consent.

Test Procedure

All patients were tested in a medication off condition following a 12-hour overnight withdrawal of dopaminergic medication. Blinded to the patients, we randomly assigned them to one of the following stimulation conditions: both electrodes switched OFF, right electrode ON and left electrode OFF, right electrode OFF and left electrode ON, and both electrodes ON. We used the identical stimulation parameters as for chronic DBS. The neurological examination (UPDRS III) began at least 30 minutes after changing the stimulation condition when a stable clinical status was achieved. The total score of the UPDRS III was calculated and in order to quantify the degree of symptom asymmetry, as well as the mean left and right sum scores of those UPDRS items (20-26) assessing lateralized symptoms. In addition, the visual attention task and the line bisection were performed in a random order. After these tests, the next stimulator settings were set and the described procedure were repeated until all four stimulation conditions were passed.

Neglect Tests

The visual attention task³¹ was run on a personal computer and took place in a dimly illuminated room. Each patient was instructed to sit 60 to 80 cm in front of the computer screen comfortably with the eyes and the body aligned to the center of the screen. Five vertically arranged white bars were presented on a 17 inch computer screen in front of a black background. Each line was 16 cm long with a diameter of 0.6 cm. A small black defect (0.6 \times 0.6 cm) randomly appeared on the lines on one of three portions: 2.5 cm from the top of the white line, in the middle, or 2.5 cm from the bottom. Therefore, the stimuli appeared on 15 positions. The patients were instructed to press the space bar of the computer keyboard as fast as possible using the index finger whenever the black defect appeared. Every test started with a short training session using 16 stimuli appearing randomly on one of the mentioned positions. On every following test phase, 80 stimuli randomly appeared 16 times on one of the five lines. The interstimulus interval was 2 to 5 seconds. In every treatment condition (both electrodes OFF, right ON but left OFF, right OFF but left

Stimulation	Right STN OFF/left STN OFF	Right OFF/left ON	Right ON/left OFF	Right ON/left ON
UPDRS III total score UPDRS left hemibody UPDRS right hemibody	$\begin{array}{c} 40.77 \pm 10.43 \\ 12.09 \pm 4.11 \\ 11.30 \pm 2.81 \end{array}$	$\begin{array}{c} 32.38 \pm 10.77 \\ 9.58 \pm 3.49 \\ 8.08 \pm 3.40 \end{array}$	31.00 ± 11.00 7.54 ± 3.01 9.67 ± 4.48	$\begin{array}{c} 24.67 \pm 9.00 \\ 6.29 \pm 2.66 \\ 6.42 \pm 3.02 \end{array}$

TABLE 1. Results of the neurological examination in four stimulation settings

UPDRS III unilateral items (20-26) were scored separately to evaluate the degree of symptom asymmetry.

ON, and both electrodes OFF), two runs were performed responding with the dominant hand and the nondominant hand, respectively, in a random order. The reaction time (RT) was measured using real-time MSDOS to ensure that responses were measured to millisecond accuracy. The mean of all RTs following the stimuli on one bar was calculated regardless of the position of stimuli on the bar (top, middle, or bottom position). To evaluate possible tendencies of lateralization, we calculated a ratio representing left-side orientation (mean RTs of the most left-sided bar/mean RTs of the middle bar) and a ratio representing right-side orientation (mean RTs of the most right-sided bar/mean RTs of middle bar). These quotients represent the allocation of attention in the absence of stimulation-influenced baseline RTs. The procedure is very sensitive to spatial attentional deficits; moreover, it is quantitative.31

The patients were tested with a line bisection task. Lines with a length of 8, 16, and 24 cm were presented on separate horizontally oriented 21×29.7 cm sheet of paper. The center of the sheets was aligned with the body's sagittal midline. Patients were asked to divide every line exactly in the middle using the dominant hand. Each length of the horizontal line bisection task was presented five times without any time limit. The deviation of the center of the line was measured with millimeter accuracy. Deviations to the left side were defined as negative values.

Statistical Analysis

Regarding the stimulation settings (stimulation voltage, frequency, and pulse width), right versus left Wilcoxon signed ranks test was used. The following data were analyzed by separate general linear model with repeated measurements using SPSS for Windows: related to the UPDRS III scores, a 4×1 factor design was calculated using the variables stimulation (right OFF/left OFF, right ON/left OFF, right OFF/left ON, and right ON/left ON) and the variable UPDRS score to assess within-subjects effects. Contrasts were used to test for differences between the levels of the factor stimulation. For the visual attention task, we chose a $4 \times 2 \times 2$ factor design using the variables stimulation (right OFF/left OFF, right ON/left OFF, right OFF/left ON, and right OFF, right ON/left OFF, right OFF/left ON, and right ON/left ON), hand (right hand and left hand), and response side (most right part of the screen and most left side of the screen) to assess within-subjects effects. Contrasts were used to test for differences between the levels of the factor stimulation, hand, and side. To assess tendencies of lateralization, we furthermore chose a 4×1 factor design using the variables stimulation (right OFF/ left OFF, right ON/left OFF, right OFF/left ON, and right ON/left ON) concerning the RT ratio for the left-sided stimuli and for the right-sided stimuli, respectively. Contrasts were used to test for differences between the levels of the factor stimulation. The results of the line bisection task were analyzed by a 4×3 factor design using the variables stimulation (right OFF/left OFF, right ON/left OFF, right OFF/left ON, and right ON/left ON) and length of the line (8, 16, and 24 cm). Again, contrasts were used to test for differences between the levels of the factors. The effect of symptom lateralization of the disease (predominantly right- and left-sided parkinsonism) on visuospatial lateralization was tested as between subject factor for the results of the visual attention task and the line bisection task separately.

RESULTS

There was no statistically significant difference between the stimulation setting comparing the right and the left electrode regarding stimulation voltage, frequency, and pulse width. One patient refused the line bisection task and the visual attention task while both stimulators were turned OFF.

UPDRS Motor Score

Tests of within-subjects effects show a significant effect of stimulation (F = 25.21; P < 0.001). Within-subjects contrasts demonstrate a significant improvement of UPDRS score of the stimulation settings turning ON one stimulator (right ON/left OFF and right OFF/left ON) compared to the stimulation settings turning OFF both stimulators (Table 1). On the other hand, within-subjects contrasts demonstrate a significant improvement of UPDRS score of the stimulation settings turning ON both sides of the stimulators (right ON/left ON) compared to the stimulation settings turning ON one stimulator exclusively (right ON/left OFF and right ON/left OFF). The UPDRS scores with the stimulator set-

TABLE 2. Ratios of the visual attention task represent
left-side orientation (left hemispace) and right-side
orientation (right hemispace) for the left hand
and the right hand separately

	Ratio of orientation		
Stimulation setting and hand tested	Left hemispace	Right hemispace	
Right OFF/left OFF			
Left hand	1.0680	1.1028	
Right hand	1.1267	1.0989	
Right OFF/left ON			
Left hand	1.2320*	1.0685*	
Right hand	1.2907*	1.0894*	
Right ON/left OFF			
Left hand	1.1591	1.0991	
Right hand	1.2425	1.1665	
Right ON/left ON			
Left hand	1.1078	1.0719	
Right hand	1.0487	1.0235	

These quotients represent the allocation of attention in the absence of stimulation influenced baseline RTs(*). Stimulation of the left electrode exclusively leads to a significant increased ratio of orientation to visual stimuli of the left hemispace. Ratio of the left-side orientation = mean RTs of the most left-side bar/mean RTs of the middle bar. Ratio of the right-side orientation = mean RTs of the most right-side bar.

ting right ON/left OFF compared to UPDRS score right OFF/left ON are not statistically different. Especially in the unilateral stimulation settings, no shift in gaze direction was found.

Visual Attention Task

Test of within-subjects effects showed a significant effect of stimulation on reaction time performance (F = 4.887; P = 0.007) and no significant effects for the variables hand and side (Fig. 1). Within-subjects contrasts identified the stimulation setting right OFF/left OFF as the significant different condition compared to the other stimulation settings. These results demonstrate significantly increased RTs when both stimulators were switched OFF. Within-subjects contrasts furthermore showed a significant interaction concerning the variables Stimulation \times Side and identified the Stimulation setting right OFF/left ON as the relevant condition significantly different from the other conditions (F =7.97; P = 0.018). To identify the stimulus side responsible for the significant interaction (Stimulation \times Side), a 4 \times 1 factor design using the variables stimulation concerning the RT ratio for the left-sided stimuli showed a significant effect for stimulation (F = 2.99; P = 0.047) (Table 2). Posthoc contrasts demonstrated a significant effect of the stimulation condition right OFF/left ON compared to the other stimulation settings (F = 5.42; P = 0.042). There were no significant effects concerning the right-side orientation. In summary, the results show significant increased RTs when both stimulators were turned OFF independently of the side of stimulus onset. The significant interaction Stimulation \times Side was the consequence of increased RTs to left-sided stimuli in the stimulation condition right OFF/ left ON. Additionally, patient results did not differ in terms of their preoperatively predominant hemiparkinsonian side acquired within the scope of the natural history of the disease.

Line Bisection Task

Testing of within-subjects effects shows a significant effect of stimulation (F = 7.06; P = 0.001) and no significant effects for the variable length of the line and



FIG. 1. Results of the visual attention task. At the top are two schemes of the screen for the right and the left hand, respectively (A). Patients should respond by pressing a bottom with the right (left part of the figure) or the left hand (right part of the figure) when a small defect appears. B to E display the reaction times (mean and standard error of the mean) responding to the lines of the scheme in four stimulations settings: (B) both stimulators turned OFF, (C) left-sided stimulator turned ON exclusively, (D) right-sided stimulator turned ON exclusively, and (E) both stimulators turned ON. Asterisk denotes significant increased reaction times.

24 cm 1.0 0.5 0.0 0.5 1.0 Deviation to the left [cm] Deviation to the right [cm] FIG. 2. Results of the line bisection task. The figure illustrates the deviations (mean and standard deviation) to the left side and to the right side of the middle. The lines of 8, 16, and 24 cm of the line bisection task are grouped concerning the following stimulation settings: (A) both stimulators turned OFF, (B) left-sided stimulator turned ON exclusively, (C) right-sided stimulator turned ON exclusively, and (D) both stimulators turned ON. Turning the left stimulator ON exclusively (B) showed a significant orientation bias to the right side compared

no interaction (Stimulation \times Length; Fig. 2). Withinsubjects contrasts identify the stimulation setting right OFF/left ON as the significant different condition compared to the other stimulation settings (F = 11.21; P = 0.007). In summary, the stimulation setting right OFF/ left ON leads to a significant orientation to the right side. The statistical analysis of the preoperatively predominant side of parkinsonian symptoms did not show any significant differences.

with the other stimulation settings shown in A, C, and D.

DISCUSSION

In patients with PD who had a symmetrical improvement of their motor symptoms with bilateral STN stimulation, an exclusively left-sided STN-DBS increased mildly the reaction times of both hands to visual stimuli of the left extrapersonal hemispace. The line bisection task showed a slight but significant visuospatial orientation toward the contralateral right side. In the other stimulation settings, including right subthalamic stimulation only, no asymmetry of space orientation was detected either in the visual attention task or in the line bisection task. Turning on the left subthalamic stimulation exclusively thus led to a neglect of left-sided stimuli. The magnitude of these results, although small, was statistically significant. These results demonstrate the influence of the STN in spatial orientation.

Previous studies have investigated the role of basal ganglia in spatial orientation. In nonparkinsonian rats, a unilateral STN lesion revealed an orientation bias toward the contralesional side.^{22,37} Lesions in the nonmotor parts of the external globus pallidus (GPe) in nonparkinsonian monkeys induced a disturbance in spatial attention interpreted as a hyperattraction toward goals in the contralateral side relative to the lesioned GPe.38 It has been argued that an imbalance in dopaminergic cortico-subcortical circuits causes a unilateral disturbance in attention and intention to the contralesional side.³⁹ According to current models of basal ganglia-thalamocortical circuits, the substantia nigra, pars compacta (SNc), modulate the activity of basal ganglia output neurons in the internal segment of the globus pallidus and the substantia nigra, pars reticularis (SNr), by an inhibitory direct striato-pallidal pathway and an indirect pathway including GPe and STN neurons.⁴⁰ Lesions in the indirect pathway (STN and GPe) decrease basal ganglia output and induce an orientation bias to the contralesional side. A reduction of dopamine release as is seen after a unilateral SNc lesion will therefore result in a net increase in basalganglia output and induce an ipsilesional orientation bias. Consequently, an additional STN lesion in a hemiparkinsonian rat reduces the orientation bias.22 High-frequency DBS generates spikes in STN neurons and block their spontaneous activity.41 These mechanisms may remove the deleterious activity of basal ganglia network in the parkinsonian state and the functional outcome of subthalamic stimulation mimics that of an STN lesion.^{23,24} Therefore, in the present study examining patients suffering from bilateral parkinsonism, one might expect a contralateral orientation bias after unilateral STN stimulation in both stimulation settings (exclusively stimulation of the right or left electrode, respectively). In opposition, our results showed an ipsilateral neglect after left-sided STN DBS. It is difficult to integrate our main finding of an ipsilateral neglect after left-sided STN stimulation in the concepts of basic science mentioned above. In animal models, pure unilateral lesions of nigrostriatal projections were used, whereas our PD patients suffered from bilateral hypokinetic syndrome. Even in a chronic 1-methyl-4-phenyl-1,2,3,6tetrahydropyridine (MPTP) model leading to a bilateral hypokinetic syndrome similar to PD in humans, core features such as a neurodegeneration outside the SN were missed.



The imbalance in cortico-subcortical circuits caused by DBS of the left STN only is similar to left hemiparkinsonism with a relative right-sided striatal hypodopaminergic state. In predominantly left-sided PD, previous studies have demonstrated a tendency to cross lines to the right of the middle,⁴² a right-sided orientation in a line-crossing-out test,43 and the directional bias of initial visual exploration.44 The neglect found after left-side stimulation exclusively is similar to signs and symptoms of neglect in predominantly left-sided PD patients reported by Lee and colleagues.⁴⁵ Also, quantitatively, both studies showed only a mild but significant neglect. The practical effect of such impairment would be small. Lee and colleagues⁴⁵ point out that patients need a long time before they bisect the line and therefore patients might use compensatory strategies in a task without any time limit. In the visual attention task, patients were under pressure of time and the magnitude of the neglect increased compared to the line bisection task. Furthermore, patients had only a short time to develop compensatory strategies in our study because none of the patients was familiar with a one-sided stimulation. These arguments are in line with the study by Lee and colleagues⁴⁵ of an underestimation of neglect in a laboratory situation compared to a situation with a higher pressure of time.

The nature of the perceptual and the motor components of signs and symptoms of neglect are still a mater of debate.^{10,46–49} Using the visual attention task in the present study, the patients were required to use the right or left hand to respond to visual stimuli from different spatial positions. This procedure allowed separate assessments of each side in each stimulation setting in order to distinguish hemispatial and hemimotor impairments. The observed neglect after left-side stimulation in our patients was detectable in the dominant and the nondominant hand in the visual attention task and in the line bisection task, too. These results suggest that left-sided STN DBS leads to a disturbance in spatial mental representation and is not the consequence of hemimotor impairment. Putamen, pulvinar, and the head of the caudate nucleus are the subcortical structures that exert perceptual spatial orientation in man.^{5,18} Damage to these structures of the right hemisphere leads to considerable signs of neglect. STN efferents to the putamen and the head of the caudate nucleus might influence spatial orientation via these subcortical nuclei.

On the other hand, imaging studies examining visual attention showed an activation of the right anterior cingulate gyrus, the intraparietal sulcus of right posterior parietal cortex, and the mesial and lateral premotor cortices.⁵⁰ Via subcortico–cortical circuits, the STN is connected with the anterior cingulate cortex.⁵¹ STN DBS seems to modulate anterior cingulate cortex activity in a task-specific manner^{27,52} and might influence spatial orientation via the projections to anterior cingulate cortex of the right hemisphere.

Animal studies revealed the influence of basal ganglia and especially the STN in oculomotor functions.53,54 Ventromedial parts of the STN projections are part of the cortico-subcortical circuits originating in the frontal eye field.53,54 Furthermore, STN efferents to substantia nigra are indirectly connected with the superior colliculi (SC) and modulate activity within the SC.55-58 Both SC and the frontal eye field are involved in saccadic eye movements, which have been described as deficient in PD patients.59 Unilateral right or left STN DBS can induce contralateral gaze deviation. It is unknown whether this is related specifically to inactivation of STN neurons or rather related to activation of neighboring supranuclear fibers.^{60,61} In our patients, conjungate eye deviations after unilateral STN stimulation was not detected on clinical evaluation with the different stimulation settings. If unilateral right or left STN stimulation produces an imbalance in the oculomotor system leading to a contralateral ocular deviation, a symmetrical neglect to the ipsilateral side should be expected. In our patients, however, neglect was detected exclusively after left-sided stimulation. This argues against the assumption that our results are the effect of an alteration in the oculomotor system.

The present study demonstrates a neglect for left-sided visual stimuli only after left-sided subthalamic stimulation in PD patients rendered hemiparkinsonian on the left side of the body. This asymmetrical manifestation of a neglect in our study can be explained by the righthemispheric lateralization of visuospatial control in human species⁶² and might be related to the right hemispheric dominance of space orientation.^{5,63}

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